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229-0014 (JP). KIMURA, Tomoko [JP/JP]; 715, 2-9-1, Kohoku, Tsuchiura-shi, Ibaraki 300-0032 (JP).

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(74) Agents: AOYAMA, Tamotsu et al.; AOYAMA & PARTNERS, IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Osaka-shi, Osaka 540-0001 (JP).

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(71) Applicants (*for all designated States except US*): PROTEGENE INC. [JP/JP]; 2-20-3, Naka-cho, Meguro-ku, Tokyo 153-0065 (JP). SAGAMI CHEMICAL RESEARCH CENTER [JP/JP]; 4-1, Nishi-Onnuma 4-chome, Sagamihara-shi, Kanagawa 229-0012 (JP).

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(72) Inventors; and

(75) Inventors/Applicants (*for US only*): KATO, Seishi [JP/JP]; 3-46-50, Wakamatsu, Sagamihara-shi, Kanagawa

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(54) Title: HUMAN PROTEINS HAVING HYDROPHOBIC DOMAINS AND DNAs ENCODING THESE PROTEINS

(57) Abstract: The present invention provides human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs, transformed eukaryotic cells expressing these DNAs and antibodies directed to these proteins.

## DESCRIPTION

Human Proteins Having Hydrophobic Domains and  
DNAs Encoding These Proteins

5

## TECHNICAL FIELD

The present invention relates to human proteins having hydrophobic domains, DNAs encoding these proteins, expression vectors for these DNAs, eukaryotic cells  
10 expressing these DNAs and antibodies directed to these proteins. The proteins of the present invention can be employed as pharmaceuticals or as antigens for preparing antibodies directed to these proteins. The human cDNAs of the present invention can be utilized as probes for genetic  
15 diagnosis and gene sources for gene therapy. Furthermore, the cDNAs can be utilized as gene sources for producing the proteins encoded by these cDNAs in large quantities. Cells into which these genes are introduced to express secretory proteins or membrane proteins in large quantities can be  
20 utilized for detection of the corresponding receptors or ligands, screening of novel small molecule pharmaceuticals and the like. The antibodies of the present invention can be utilized for the detection, quantification, purification and the like of the proteins of the present invention.

25

## BACKGROUND ART

Cells secrete many proteins extracellularly. These secretory proteins play important roles in the proliferation control, the differentiation induction, the material transport, the biophylaxis, and the like of the cells. Unlike intracellular proteins, the secretory proteins exert their actions outside the cells. Therefore, they can be administered in the intracorporeal manner such as the injection or the drip, and they possess hidden potentialities as pharmaceuticals. In fact, a number of human secretory proteins such as interferons, interleukins, erythropoietin, thrombolytic agents and the like are currently employed as pharmaceuticals. In addition, secretory proteins other than those described above are undergoing clinical trials for developing their use as pharmaceuticals. It is believed that the human cells produce many unknown secretory proteins. Availability of these secretory proteins as well as genes encoding them is expected to lead to development of novel pharmaceuticals utilizing them.

On the other hand, membrane proteins play important roles, as signal receptors, ion channels, transporters and the like, in the material transport and the signal transduction through the cell membrane. Examples thereof include receptors for various cytokines, ion

channels for the sodium ion, the potassium ion, the chloride ion and the like, transporters for saccharides, amino acids and the like. The genes for many of them have already been cloned. It has been clarified that abnormalities in these  
5 membrane proteins are involved in a number of previously cryptogenic diseases. Therefore, discovery of a new membrane protein is expected to lead to elucidation of the causes of many diseases, and isolation of new genes encoding the membrane proteins has been desired.

10           Heretofore, due to difficulty in the purification from human cells, many of these secretory proteins and membrane proteins have been isolated by genetic approaches. A general method is the so-called expression cloning method, in which a cDNA library is introduced into eukaryotic cells  
15 to express cDNAs, and the cells secreting, or expressing on the surface of membrane, the protein having the activity of interest are then screened. However, only genes for proteins with known functions can be cloned by using this method.

          In general, a secretory protein or a membrane  
20 protein possesses at least one hydrophobic domain within the protein. After synthesis on ribosomes, such domain works as a secretory signal or remains in the phospholipid membrane to be entrapped in the membrane. Accordingly, if the existence of a highly hydrophobic domain is observed in the  
25 amino acid sequence of a protein encoded by a cDNA when the

whole base sequence of the full-length cDNA is determined, it is considered that the cDNA encodes a secretory protein or a membrane protein.

## 5 OBJECTS OF INVENTION

The main object of the present invention is to provide novel human proteins having hydrophobic domains, DNAs coding for these proteins, expression vectors for these DNAs, transformed eucaryotic cells that are capable of  
10 expressing these DNAs and antibodies directed to these proteins.

## SUMMARY OF INVENTION

As the result of intensive studies, the present  
15 inventors have successfully cloned cDNAs encoding proteins having hydrophobic domains from the human full-length cDNA bank, thereby completing the present invention. Thus, the present invention provides a human protein having hydrophobic domain(s), namely a protein comprising any one  
20 of amino acid sequences selected from the group consisting of SEQ ID NOS: 1 to 10, 31 to 40, 61 to 70, 91 to 100 and 121 to 130. Moreover, the present invention provides a DNA encoding said protein, exemplified by a cDNA comprising any one of base sequences selected from the group consisting of  
25 SEQ ID NOS: 11 to 30, 41 to 60, 71 to 90, 101 to 120 and 131

to 150, an expression vector that is capable of expressing said DNA by in vitro translation or in eukaryotic cells, a transformed eukaryotic cell that is capable of expressing said DNA and of producing said protein, and an antibody  
5 directed to said protein.

This object as well as other objects and advantages of the present invention will become apparent to those skilled in the art from the following description with reference to the accompanying drawings.

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#### BRIEF DESCRIPTION OF DRAWINGS

Figure 1: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03613.

15 Figure 2: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03700.

Figure 3: A figure depicting the hydrophobicity/hydrophilicity profile of the protein  
20 encoded by clone HP03935.

Figure 4: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10755.

Figure 5: A figure depicting the hydrophobicity/hydrophilicity profile of the protein  
25

encoded by clone HP10760.

Figure 6: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10764.

5 Figure 7: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10768.

Figure 8: A figure depicting the hydrophobicity/hydrophilicity profile of the protein  
10 encoded by clone HP10769.

Figure 9: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10784.

Figure 10: A figure depicting the hydrophobicity/hydrophilicity profile of the protein  
15 encoded by clone HP10786.

Figure 11: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03727.

20 Figure 12: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03801.

Figure 13: A figure depicting the hydrophobicity/hydrophilicity profile of the protein  
25 encoded by clone HP03883.

Figure 14: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03913.

5 Figure 15: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10753.

Figure 16: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10758.

10 Figure 17: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10771.

15 Figure 18: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10778.

Figure 19: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10781.

20 Figure 20: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10785.

Figure 21: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03878.

25 Figure 22: A figure depicting the



hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03884.

Figure 23:A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03934.

Figure 24: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03949.

Figure 25: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03959.

Figure 26: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03983.

Figure 27: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10745.

Figure 28: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10775.

Figure 29: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10782.

Figure 30:A figure depicting the hydrophobicity/hydrophilicity profile of the protein.

Figure 31:A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03977.

5 Figure 32:A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10649.

Figure 33:A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10779.

10 Figure 34: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10790.

15 Figure 35: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10793.

Figure 36: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10794.

20 Figure 37: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10797.

Figure 38: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10798.

25 Figure 39: A figure depicting the

hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10800.

Figure 40:A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10801.

Figure 41:A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03596.

Figure 42:A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03882.

Figure 43:A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03903.

Figure 44: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03974.

Figure 45: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03978.

Figure 46: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10735.

Figure 47: A figure depicting the hydrophobicity/hydrophilicity profile of the protein

encoded by clone HP10750.

Figure 48: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10777.

5 Figure 49: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10780.

10 Figure 50: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10795.

#### DETAILED DESCRIPTION OF THE INVENTION

The proteins of the present invention can be obtained, for example, by a method for isolating proteins from human organs, cell lines or the like, a method for preparing peptides by the chemical synthesis based on the amino acid sequence of the present invention, or a method for producing proteins by the recombinant DNA technology using the DNAs encoding the hydrophobic domains of the present invention. Among these, the method for producing proteins by the recombinant DNA technology is preferably employed. For example, the proteins can be expressed in vitro by preparing an RNA by in vitro transcription from a vector having the cDNA of the present invention, and then carrying out in vitro translation using this RNA as a

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20

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template. Alternatively, incorporation of the translated region into a suitable expression vector by the method known in the art may lead to expression of the encoded protein in large quantities in prokaryotic cells such as *Escherichia coli* and *Bacillus subtilis*, or eukaryotic cells such as yeasts, insect cells and mammalian cells.

In the case where the protein of the present invention is produced by expressing the DNA by in vitro translation, the protein of the present invention can be produced in vitro by incorporating the translated region of this cDNA into a vector having an RNA polymerase promoter, and then adding the vector to an in vitro translation system such as a rabbit reticulocyte lysate or a wheat germ extract, which contains an RNA polymerase corresponding to the promoter. The RNA polymerase promoters are exemplified by T7, T3, SP6 and the like. The vectors containing promoters for these RNA polymerases are exemplified by pKA1, pCDM8, pT3/T7 18, pT7/3 19, pBluescript II and the like. Furthermore, the protein of the present invention can be expressed in the secreted form or the form incorporated in the microsome membrane when a canine pancreas microsome or the like is added to the reaction system.

In the case where the protein of the present invention is produced by expressing the DNA in a microorganism such as *Escherichia coli*, a recombinant

expression vector in which the translated region of the cDNA of the present invention is incorporated into an expression vector having an origin which is capable of replicating in the microorganism, a promoter, a ribosome-binding site, a cDNA-cloning site, a terminator and the like is constructed. After transformation of the host cells with this expression vector, the resulting transformant is cultured. Thus, the protein encoded by the cDNA can be produced in large quantities in the microorganism. In this case, a protein fragment containing any translated region can be obtained by adding an initiation codon and a termination codon in front of and behind the selected translated region and expressing the protein. Alternatively, the protein can be expressed as a fusion protein with another protein. Only the portion of the protein encoded by the cDNA can be obtained by cleaving this fusion protein with a suitable protease. The expression vectors for *Escherichia coli* are exemplified by the pUC series, pBluescript II, the pET expression system, the pGEX expression system and the like.

In the case where the protein of the present invention is produced by expressing the DNA in eukaryotic cells, the protein of the present invention can be produced as a secretory protein, or as a membrane protein on the surface of cell membrane, by incorporating the translated region of the cDNA into an expression vector for eukaryotic

cells that has a promoter, a splicing region, a poly(A) addition site and the like, and then introducing the vector into the eukaryotic cells. The expression vectors are exemplified by pKA1, pED6dpc2, pCDM8, pSVK3, pMSG, pSVL, 5 pBK-CMV, pBK-RSV, EBV vectors, pRS, pYES2 and the like. Examples of eukaryotic cells to be used in general include mammalian cultured cells such as monkey kidney COS7 cells and Chinese hamster ovary CHO cells, budding yeasts, fission yeasts, silkworm cells, and Xenopus oocytes. Any eukaryotic 10 cells may be used as long as they are capable of expressing the proteins of the present invention. The expression vector can be introduced into the eukaryotic cells by using a method known in the art such as the electroporation method, the calcium phosphate method, the liposome method and the 15 DEAE-dextran method.

After the protein of the present invention is expressed in prokaryotic cells or eukaryotic cells, the protein of interest can be isolated and purified from the culture by a combination of separation procedures known in 20 the art. Examples of the separation procedures include treatment with a denaturing agent such as urea or a detergent, sonication, enzymatic digestion, salting-out or solvent precipitation, dialysis, centrifugation, ultrafiltration, gel filtration, SDS-PAGE, isoelectric 25 focusing, ion-exchange chromatography, hydrophobic

chromatography, affinity chromatography and reverse phase chromatography.

The proteins of the present invention also include peptide fragments (of 5 amino acid residues or more) containing any partial amino acid sequences in the amino acid sequences represented by SEQ ID NOS: 1 to 10, 31 to 40, 61 to 70, 91 to 100 and 121 to 130. These peptide fragments can be utilized as antigens for preparation of antibodies. Among the proteins of the present invention, those having the signal sequences are secreted in the form of mature proteins after the signal sequences are removed. Therefore, these mature proteins shall come within the scope of the protein of the present invention. The N-terminal amino acid sequences of the mature proteins can be easily determined by using the method for the determination of cleavage site of a signal sequence [JP-A 8-187100]. Furthermore, some membrane proteins undergo the processing on the cell surface to be converted to the secreted forms. Such proteins or peptides in the secreted forms shall also come within the scope of the protein of the present invention. In the case where sugar chain-binding sites are present in the amino acid sequences of the proteins, expression of the proteins in appropriate eukaryotic cells affords the proteins to which sugar chains are added. Accordingly, such proteins or peptides to which sugar chains are added shall also come



within the scope of the protein of the present invention.

The DNAs of the present invention include all the DNAs encoding the above-mentioned proteins. These DNAs can be obtained by using a method for chemical synthesis, a  
5 method for cDNA cloning and the like.

The cDNAs of the present invention can be cloned, for example, from cDNA libraries derived from the human cells. The cDNAs are synthesized by using poly(A)<sup>+</sup> RNAs extracted from human cells as templates. The human cells may  
10 be cells delivered from the human body, for example, by the operation or may be the cultured cells. The cDNAs can be synthesized by using any method such as the Okayama-Berg method [Okayama, H. and Berg, P., Mol. Cell. Biol. 2: 161-170 (1982)], the Gubler-Hoffman method [Gubler, U. and  
15 Hoffman, J., Gene 25: 263-269 (1983)] and the like. However, it is desirable to use the capping method [Kato, S. et al., Gene 150: 243-250 (1994)], as exemplified in Examples, in order to obtain a full-length clone in an effective manner. In addition, commercially available human cDNA libraries can  
20 be utilized. The cDNAs of the present invention can be cloned from the cDNA libraries by synthesizing an oligonucleotide on the basis of base sequences of any portion in the cDNA of the present invention and screening the cDNA libraries using this oligonucleotide as a probe for  
25 colony or plaque hybridization according to a method known

in the art. In addition, the cDNA fragments of the present invention can be prepared from an mRNA isolated from human cells by the RT-PCR method in which oligonucleotides which hybridize with both termini of the cDNA fragment of interest  
5 are synthesized, which are then used as the primers.

The cDNAs of the present invention are characterized in that they comprise any one of the base sequences represented by SEQ ID NOS: 11 to 20, 41 to 50, 71 to 80, 101 to 110 and 131 to 140 or the base sequences  
10 represented by SEQ ID NOS: 21 to 30, 51 to 60, 81 to 90, 111 to 120 and 141 to 150. Table 1 summarizes the clone number (HP number), the cells from which the cDNA clone was obtained, the total number of bases of the cDNA, and the number of the amino acid residues of the encoded protein,  
15 for each of the cDNAs.

Table 1

Sequence No.	HP No.	Cell	Number of bases	Number of amino acids
1, 11, 21	HP03613	Kidney	2865	578
2, 12, 22	HP03700	Kidney	3323	243
3, 13, 23	HP03935	Kidney	1585	461
4, 14, 24	HP10755	Kidney	2122	647
5, 15, 25	HP10760	Kidney	1775	446
6, 16, 26	HP10764	Kidney	1372	197
7, 17, 27	HP10768	Kidney	2074	540
8, 18, 28	HP10769	Kidney	2252	442
9, 19, 29	HP10784	Kidney	1461	262
10, 20, 30	HP10786	Kidney	1122	152
31, 41, 51	HP03727	Kidney	1617	335
32, 42, 52	HP03801	Umbilical cord blood	1749	208
33, 43, 53	HP03883	Kidney	1402	406
34, 44, 54	HP03913	Kidney	2474	618
35, 45, 55	HP10753	Umbilical cord blood	3296	208
36, 46, 56	HP10758	Kidney	1818	502
37, 47, 57	HP10771	Kidney	1646	336
38, 48, 58	HP10778	Kidney	1416	340
39, 49, 59	HP10781	Kidney	1927	223
40, 50, 60	HP10785	Kidney	1419	309
61, 71, 81	HP03878	Kidney	2016	599
62, 72, 82	HP03884	Kidney	1446	81
63, 73, 83	HP03934	Kidney	2467	654
64, 74, 84	HP03949	Kidney	1450	390
65, 75, 85	HP03959	Kidney	1897	452

invention can be easily obtained by screening the cDNA libraries constructed from the human cell lines or human tissues utilized in the present invention using an oligonucleotide probe synthesized on the basis of the base  
5 sequence of the cDNA provided in any one of SEQ ID NOS: 11 to 30, 41 to 60, 71 to 90, 101 to 120 and 131 to 150.

In general, the polymorphism due to the individual differences is frequently observed in human genes. Accordingly, any cDNA in which one or plural nucleotides are  
10 added, deleted and/or substituted with other nucleotides in SEQ ID NOS: 11 to 30, 41 to 60, 71 to 90, 101 to 120 and 131 to 150 shall come within the scope of the present invention.

Similarly, any protein in which one or plural amino acids are added, deleted and/or substituted with other  
15 amino acids resulting from the above-mentioned changes shall come within the scope of the present invention, as long as the protein possesses the activity of the protein having any one of the amino acid sequences represented by SEQ ID NOS: 1 to 10, 31 to 40, 61 to 70, 91 to 100 and 121 to 130.

20 The cDNAs of the present invention also include cDNA fragments (of 10 bp or more) containing any partial base sequence in the base sequences represented by SEQ ID NOS: 11 to 20, 41 to 50, 71 to 80, 101 to 110 and 131 to 140 or in the base sequences represented by SEQ ID NOS: 21 to 30,  
25 51 to 60, 81 to 90, 111 to 120 and 141 to 150. Also, DNA

fragments each consisting of a sense strand and an anti-sense strand shall come within this scope. These DNA fragments can be utilized as the probes for the genetic diagnosis.

5           The antibody of the present invention can be obtained from a serum after immunizing an animal using the protein of the present invention as an antigen. A peptide that is chemically synthesized based on the amino acid sequence of the present invention and a protein expressed in  
10   eukaryotic or prokaryotic cells can be used as an antigen. Alternatively, an antibody can be prepared by introducing the above-mentioned expression vector for eukaryotic cells into the muscle or the skin of an animal by injection or by using a gene gun and then collecting a serum therefrom [JP-A  
15   7-313187]. Animals that can be used include a mouse, a rat, a rabbit, a goat, a chicken and the like. A monoclonal antibody directed to the protein of the present invention can be produced by fusing B cells collected from the spleen of the immunized animal with myelomas to generate hybridomas.

20           In addition to the activities and uses described above, the polynucleotides and proteins of the present invention may exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for  
25   proteins of the present invention may be provided by

administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

5                   Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or  
10 therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome  
15 markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive  
20 PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise  
25 anti-protein antibodies using DNA immunization techniques;

and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction),  
5 the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

10 The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled  
15 reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or  
20 development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding  
25 occurs or to identify inhibitors of the binding interaction.

base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA42490) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10760> (SEQ ID NOS: 5, 15, and 25)

Determination of the whole base sequence of the cDNA insert of clone HP10760 obtained from cDNA library of human kidney revealed the structure consisting of a 61-bp 5'-untranslated region, a 1341-bp ORF, and a 373-bp 3'-untranslated region. The ORF encodes a protein consisting of 446 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 5 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 48 kDa that was somewhat smaller than the molecular weight of 49,468 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 50 kDa. In addition, there exists in the amino acid sequence of this protein two sites at which N-glycosylation may occur (Asn-Ala-Thr at position 144 and Asn-Ile-Ser at position 243). Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal



sequence, allows to expect that the mature protein starts from glutamic acid at position 27.

The search of the protein database using the amino acid sequence of the present protein revealed that the protein was similar to human 25 kDa trypsin inhibitor (Accession No. BAA25066). Table 6 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and human 25 kDa trypsin inhibitor (TI). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 33.5% in the intermediate region of 185 amino acid residues.

15

Table 6

HP	MLHPETSPGRGHLLAVLLALLGTAWAEVWPPQLQEAPMAG
TI	MIAISAVSSALLFSLCEASTVLLNSTDSSPPTNNFTDIEAALKAQLDSADIPKARRKR
HP	ALNRKESFLLLSLHNRLRSWVQPPAADMRRLDWSLSLAQLAQAALCGIPTPSLASGLW
	..... . *. **.*. * ****.* . *...**. *.**.* * * ... . * *
TI	YISQNDMIAILDYHNQVRGKVFPPAANMEYMWVDENLAKSAEAWAATC-IWDHG-PSYLL

25

HP RTLQVGWNMQLLPAGLASFVEVSLWFAEGQRYSHA-AGEC-----AR-NATCTHYTQL

\* \* . . . . . \* . . . . \* . . . . \* . . . . \* . . . . \*

TI RFLGQN---LSVRTGRYRSILQLVKPWYDEVKDYAFPYPQDCNPRCPMRCFGPMCTHYTQM

5 HP VWATSSQLGCCGRHLCSAGQA---AI---EAF-VCAYSPGGNWEVNGKTIIPYKKGAWCSLC

\*\*\*\*\*...\*. \* \* . . . . . \* . . . . \* . . . . \* . . . . \*

TI VWATSNRIGCAIHTCQNMNVWGSVWRRAYLVCNYAPKGNW---IGEA---PYKVGVPCCSSC

HP TASVSGCFKAWDHAGGLCEVPRNPCRMSQNHGRLNISTCHCHCPPGYTGTRYCQVRCSLQ

10 . . \* . \*

TI PPSYGGSCDNLCPFVTSNYLYWFK

The search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI792411) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

20 <HP10764> (SEQ ID NOS: 6, 16, and 26)

Determination of the whole base sequence of the cDNA insert of clone HP10764 obtained from cDNA library of human kidney revealed the structure consisting of a 326-bp 5'-untranslated region, a 594-bp ORF, and a 452-bp 3'-untranslated region. The ORF encodes a protein consisting of

12 / 346

500 505 510  
Leu Ala Val Gly Ala Ala Phe Ala Ser Ser Trp Lys Thr Gly Leu Ala  
515 520 525  
Thr Ser Leu Ala Val Phe Cys His Glu Leu Pro His Glu Leu Gly Asp  
5 530 535 540  
Phe Ala Ala Leu Leu His Ala Gly Leu Ser Val Arg Gln Ala Leu Leu  
545 550 555 560  
Leu Asn Leu Ala Ser Ala Leu Thr Ala Phe Ala Gly Leu Tyr Val Ala  
565 570 575  
10 Leu Ala Val Gly Val Ser Glu Glu Ser Glu Ala Trp Ile Leu Ala Val  
580 585 590  
Ala Thr Gly Leu Phe Leu Tyr Val Ala Leu Cys Asp Met Leu Pro Ala  
595 600 605  
Met Leu Lys Val Arg Asp Pro Arg Pro Trp Leu Leu Phe Leu Leu His  
15 610 615 620  
Asn Val Gly Leu Leu Gly Gly Trp Thr Val Leu Leu Leu Leu Ser Leu  
625 630 635 640  
Tyr Glu Asp Asp Ile Thr Phe  
645  
20  
<210> 5  
<211> 446  
<212> PRT  
<213> Homo sapiens  
25 <400> 5

13 / 346

Met Leu His Pro Glu Thr Ser Pro Gly Arg Gly His Leu Leu Ala Val  
 1 5 10 15  
 Leu Leu Ala Leu Leu Gly Thr Ala Trp Ala Glu Val Trp Pro Pro Gln  
 20 25 30  
 5 Leu Gln Glu Gln Ala Pro Met Ala Gly Ala Leu Asn Arg Lys Glu Ser  
 35 40 45  
 Phe Leu Leu Leu Ser Leu His Asn Arg Leu Arg Ser Trp Val Gln Pro  
 50 55 60  
 Pro Ala Ala Asp Met Arg Arg Leu Asp Trp Ser Asp Ser Leu Ala Gln  
 10 65 70 75 80  
 Leu Ala Gln Ala Arg Ala Ala Leu Cys Gly Ile Pro Thr Pro Ser Leu  
 85 90 95  
 Ala Ser Gly Leu Trp Arg Thr Leu Gln Val Gly Trp Asn Met Gln Leu  
 100 105 110  
 15 Leu Pro Ala Gly Leu Ala Ser Phe Val Glu Val Val Ser Leu Trp Phe  
 115 120 125  
 Ala Glu Gly Gln Arg Tyr Ser His Ala Ala Gly Glu Cys Ala Arg Asn  
 130 135 140  
 Ala Thr Cys Thr His Tyr Thr Gln Leu Val Trp Ala Thr Ser Ser Gln  
 20 145 150 155 160  
 Leu Gly Cys Gly Arg His Leu Cys Ser Ala Gly Gln Ala Ala Ile Glu  
 165 170 175  
 Ala Phe Val Cys Ala Tyr Ser Pro Gly Gly Asn Trp Glu Val Asn Gly  
 180 185 190  
 25 Lys Thr Ile Ile Pro Tyr Lys Lys Gly Ala Trp Cys Ser Leu Cys Thr

14 / 346

	195	200	205
	Ala Ser Val Ser Gly Cys Phe Lys Ala Trp Asp His Ala Gly Gly Leu		
	210	215	220
	Cys Glu Val Pro Arg Asn Pro Cys Arg Met Ser Cys Gln Asn His Gly		
5	225	230	235
	Arg Leu Asn Ile Ser Thr Cys His Cys His Cys Pro Pro Gly Tyr Thr		
	245	250	255
	Gly Arg Tyr Cys Gln Val Arg Cys Ser Leu Gln Cys Val His Gly Arg		
	260	265	270
10	Phe Arg Glu Glu Glu Cys Ser Cys Val Cys Asp Ile Gly Tyr Gly Gly		
	275	280	285
	Ala Gln Cys Ala Thr Lys Val His Phe Pro Phe His Thr Cys Asp Leu		
	290	295	300
	Arg Ile Asp Gly Asp Cys Phe Met Val Ser Ser Glu Ala Asp Thr Tyr		
15	305	310	315
	Tyr Arg Ala Arg Met Lys Cys Gln Arg Lys Gly Gly Val Leu Ala Gln		
	325	330	335
	Ile Lys Ser Gln Lys Val Gln Asp Ile Leu Ala Phe Tyr Leu Gly Arg		
	340	345	350
20	Leu Glu Thr Thr Asn Glu Val Ile Asp Ser Asp Phe Glu Thr Arg Asn		
	355	360	365
	Phe Trp Ile Gly Leu Thr Tyr Lys Thr Ala Lys Asp Ser Phe Arg Trp		
	370	375	380
	Ala Thr Gly Glu His Gln Ala Phe Thr Ser Phe Ala Phe Gly Gln Pro		
25	385	390	395
			400

15 /346

Asp Asn His Gly Phe Gly Asn Cys Val Glu Leu Gln Ala Ser Ala Ala

405

410

415

Phe Asn Trp Asn Asn Gln Arg Cys Lys Thr Arg Asn Arg Tyr Ile Cys

420

425

430

5 Gln Phe Ala Gln Glu His Ile Ser Arg Trp Gly Pro Gly Ser

435

440

445

&lt;210&gt; 6

&lt;211&gt; 197

10 &lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 6

Met Pro Pro Ala Gly Leu Arg Arg Ala Ala Pro Leu Thr Ala Ile Ala

1

5

10

15

15 Leu Leu Val Leu Gly Ala Pro Leu Val Leu Ala Gly Glu Asp Cys Leu

20

25

30

Trp Tyr Leu Asp Arg Asn Gly Ser Trp His Pro Gly Phe Asn Cys Glu

35

40

45

Phe Phe Thr Phe Cys Cys Gly Thr Cys Tyr His Arg Tyr Cys Cys Arg

20

50

55

60

Asp Leu Thr Leu Leu Ile Thr Glu Arg Gln Gln Lys His Cys Leu Ala

65

70

75

80

Phe Ser Pro Lys Thr Ile Ala Gly Ile Ala Ser Ala Val Ile Leu Phe

85

90

95

25 Val Ala Val Val Ala Thr Thr Ile Cys Cys Phe Leu Cys Ser Cys Cys

29 / 346

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catagccacg ggggccacag ccacgggtgtg tccctgcagc tggcaccag cgagctccgg 1380  
cagcccaagc cccccacga gggctccgc gcagacctgg tggcggagga gagccggag 1440  
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15 &lt;210&gt; 15

&lt;211&gt; 1341

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 15

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ctggctcaag ccagggcagc cctctgtgga atccaaccc cgagcctggc gtccggcctg 300  
25 tggcgcaccc tgcaagtggg ctggaacatg cagctgctgc ccgcgggctt ggcgtccttt 360

30 / 346

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ctgggctgtg ggcggcacct gtgctctgca ggccaggcag cgatagaagc ctttgtctgt 540  
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caagtgaggt gcagcctgca gtgtgtgcac ggccggttcc gggaggagga gtgctcgtgc 840  
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&lt;210&gt; 16

20 &lt;211&gt; 594

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 16

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25 ggggctcccc tgggtgctggc cggcgaggac tgctgtggt acctggaccg gaatggctcc 120



54 / 346

	630	635	640	
	gag gat gac atc acc ttc tgataccctg ccctagtccc ccacctttga			2026
	Glu Asp Asp Ile Thr Phe			
	645			
5	cttaagatcc cacacctcac aaacctacag ccagaaaacc agaagcccct atagaggccc			2086
	cagtcccaac tccagtaaag acactcttgt ccttgg			2122
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	Met Leu His Pro Glu Thr Ser Pro Gly Arg Gly His Leu Leu Ala Val			
	1	5	10	15
20	ctc ctg gcc ctc ctt ggc acc gcc tgg gca gag gtg tgg cca ccc cag			157
	Leu Leu Ala Leu Leu Gly Thr Ala Trp Ala Glu Val Trp Pro Pro Gln			
	20	25	30	
	ctg cag gag cag gct ccg atg gcc gga gcc ctg aac agg aag gag agt			205
	Leu Gln Glu Gln Ala Pro Met Ala Gly Ala Leu Asn Arg Lys Glu Ser			
25	35	40	45	

55 /346

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 Phe Leu Leu Leu Ser Leu His Asn Arg Leu Arg Ser Trp Val Gln Pro  
 50 55 60  
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 5 Pro Ala Ala Asp Met Arg Arg Leu Asp Trp Ser Asp Ser Leu Ala Gln  
 65 70 75 80  
 ctg gct caa gcc agg gca gcc ctc tgt gga atc cca acc ccg agc ctg 349  
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 85 90 95  
 10 gcg tcc ggc ctg tgg cgc acc ctg caa gtg ggc tgg aac atg cag ctg 397  
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 100 105 110  
 ctg ccc gcg ggc ttg gcg tcc ttt gtt gaa gtg gtc agc cta tgg ttt 445  
 Leu Pro Ala Gly Leu Ala Ser Phe Val Glu Val Val Ser Leu Trp Phe  
 15 115 120 125  
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 Ala Glu Gly Gln Arg Tyr Ser His Ala Ala Gly Glu Cys Ala Arg Asn  
 130 135 140  
 gcc acc tgc acc cac tac acg cag ctc gtg tgg gcc acc tca agc cag 541  
 20 Ala Thr Cys Thr His Tyr Thr Gln Leu Val Trp Ala Thr Ser Ser Gln  
 145 150 155 160  
 ctg ggc tgt ggg cgg cac ctg tgc tct gca ggc cag gca gcg ata gaa 589  
 Leu Gly Cys Gly Arg His Leu Cys Ser Ala Gly Gln Ala Ala Ile Glu  
 165 170 175  
 25 gcc ttt gtc tgt gcc tac tcc ccc gga ggc aac tgg gag gtc aac ggg 637

56 /346

Ala Phe Val Cys Ala Tyr Ser Pro Gly Gly Asn Trp Glu Val Asn Gly  
180 185 190  
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Lys Thr Ile Ile Pro Tyr Lys Lys Gly Ala Trp Cys Ser Leu Cys Thr  
5 195 200 205  
gcc agt gtc tca ggc tgc ttc aaa gcc tgg gac cat gca ggg ggg ctc 733  
Ala Ser Val Ser Gly Cys Phe Lys Ala Trp Asp His Ala Gly Gly Leu  
210 215 220  
tgt gag gtc ccc agg aat cct tgt cgc atg agc tgc cag aac cat gga 781  
10 Cys Glu Val Pro Arg Asn Pro Cys Arg Met Ser Cys Gln Asn His Gly  
225 230 235 240  
cgt ctc aac atc agc acc tgc cac tgc cac tgt ccc cct ggc tac acg 829  
Arg Leu Asn Ile Ser Thr Cys His Cys His Cys Pro Pro Gly Tyr Thr  
245 250 255  
15 ggc aga tac tgc caa gtg agg tgc agc ctg cag tgt gtg cac ggc cgg 877  
Gly Arg Tyr Cys Gln Val Arg Cys Ser Leu Gln Cys Val His Gly Arg  
260 265 270  
ttc cgg gag gag gag tgc tcg tgc gtc tgt gac atc ggc tac ggg gga 925  
Phe Arg Glu Glu Glu Cys Ser Cys Val Cys Asp Ile Gly Tyr Gly Gly  
20 275 280 285  
gcc cag tgt gcc acc aag gtg cat ttt ccc ttc cac acc tgt gac ctg 973  
Ala Gln Cys Ala Thr Lys Val His Phe Pro Phe His Thr Cys Asp Leu  
290 295 300  
agg atc gac gga gac tgc ttc atg gtg tct tca gag gca gac acc tat 1021  
25 Arg Ile Asp Gly Asp Cys Phe Met Val Ser Ser Glu Ala Asp Thr Tyr

57 / 346

	305	310	315	320	
	tac aga gcc agg atg aaa tgt cag agg aaa ggc ggg gtg ctg gcc cag	1069			
	Tyr Arg Ala Arg Met Lys Cys Gln Arg Lys Gly Gly Val Leu Ala Gln				
	325	330	335		
5	atc aag agc cag aaa gtg cag gac atc ctc gcc ttc tat ctg ggc cgc	1117			
	Ile Lys Ser Gln Lys Val Gln Asp Ile Leu Ala Phe Tyr Leu Gly Arg				
	340	345	350		
	ctg gag acc acc aac gag gtg att gac agt gac ttc gag acc agg aac	1165			
	Leu Glu Thr Thr Asn Glu Val Ile Asp Ser Asp Phe Glu Thr Arg Asn				
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	ttc tgg atc ggg ctc acc tac aag acc gcc aag gac tcc ttc cgc tgg	1213			
	Phe Trp Ile Gly Leu Thr Tyr Lys Thr Ala Lys Asp Ser Phe Arg Trp				
	370	375	380		
	gcc aca ggg gag cac cag gcc ttc acc agt ttt gcc ttt ggg cag cct	1261			
15	Ala Thr Gly Glu His Gln Ala Phe Thr Ser Phe Ala Phe Gly Gln Pro				
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	gac aac cac ggg ttt ggc aac tgc gtg gag ctg cag gct tca gct gcc	1309			
	Asp Asn His Gly Phe Gly Asn Cys Val Glu Leu Gln Ala Ser Ala Ala				
	405	410	415		
20	ttc aac tgg aac aac cag cgc tgc aaa acc cga aac cgt tac atc tgc	1357			
	Phe Asn Trp Asn Asn Gln Arg Cys Lys Thr Arg Asn Arg Tyr Ile Cys				
	420	425	430		
	cag ttt gcc cag gag cac atc tcc cgg tgg ggc cca ggg tcc	1399			
	Gln Phe Ala Gln Glu His Ile Ser Arg Trp Gly Pro Gly Ser				
25	435	440	445		

58 /346

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&lt;210&gt; 26

10 &lt;211&gt; 1372

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; CDS

15 &lt;222&gt; (327)..(920)

&lt;400&gt; 26

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 tcgctggtgg gtggactcct gggcgctgcg cggagccgcg ccggctgggt tagcgcgggc 180  
 20 ggggcgctta gtcccacccc cagaggaggc ggaagaggag cccgagcctg gccgcgggct 240  
 gggccccgcc gcagctccag ctggccgggt tggtoctgcg gtcccttctc tgggaggccc 300  
 gaccccggcc gcgccagcc cccacc atg cca ccc gcg ggg ctc cgc cgg gcc 353

Met Pro Pro Ala Gly Leu Arg Arg Ala

1

5

25 gcg ccg ctc acc gca atc gct ctg ttg gtg ctg ggg gct ccc ctg gtg 401